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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,538	08/01/2005	Achim Feurer	Le A 35 926	8774
7590 11/17/2005				
Bayer Pharmaceuticals Corporation		EXAMINER		
400 Morgan Lane		RAO, DEEPAK R		
West Haven, CT 06516				
		ART UNIT		PAPER NUMBER
		1624		

DATE MAILED: 11/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/521,538	FEURER ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 January 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 6-12 are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-12 are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>01142005</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-4 and 6-12 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 6-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making compounds of formula (I) and the corresponding pharmaceutically acceptable salts, does not reasonably provide enablement for making a solvate of the compound of formula (I) and/or solvate of the salt thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

Factual Basis:

1. Specification has no working example of solvate of compound of formula (I); and some of the exemplified compounds within the claimed genus were in contact with solvent. Yet they have not formed solvate as evident from spectral data provided for these compounds.
2. Searching the pertinent art in the related pyrimidine area did not result in support for such solvates of instant pyrimidine compounds. Searching the more general area of solvates resulted in pertinent reference West applied below. West clearly shows lack of predictability of the art in the solvate area.

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Based on these two facts, a scope of enablement rejection follows using relevant Wands factors. Hence, the burden of establishing the *prime facie* case is met with.

Scope of enablement rejection:

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to compound of formula I, or a pharmaceutically acceptable salt or solvate thereof. Specification is not adequately enabled as to how to make solvate of compounds of formula (I) Specification has no example of solvate of the instant compounds. Specification on page 5 recites that 'solvate of a compound of formula (I) is the composition of the compound and a solvent e.g., water, ethanol' but there is no enabling disclosure of such hydrates or solvates.

The compound of formula I embrace substituted pyrimidine compounds substituted with variable group R¹. Careful calculation of the number of compounds embraced in the instant formula I shows a large number of compounds. The term "substituted" embraces undefined number of variable groups and thus, the genus embraced by claim1 is excessively large and there is no teaching of any solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that

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is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate. In the instant case of solvate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to water.

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of solvates is unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

2. The predictability or lack thereof in the art:

Hence the solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

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3. The amount of direction or guidance present:

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of solvate of instant compound. Many of the exemplified compounds were shown in the specification that have come in contact with water and/or other solvent but there is showing that these compounds formed solvates. Hence it is clear that merely bringing the compound and water or solvent together does not result in solvate and additional direction or guidance is needed to make them - specification has no such direction or guidance.

4. The presence or absence of working examples:

There is no working example of any solvate formed. The claims are drawn to solvate, yet the numerous examples presented all failed to produce a solvate or even solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be showing supporting that solvates of these compounds exists and therefore can be made.

5. The breadth of the claims & the quantity of experimentation needed:

Specification provides no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired solvate of the compound of formula I. As noted above, the

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genus embraces a large number of compounds and hence the claims are extremely broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvate of compound of formula I embraced in the instant claims in view of the pertinent reference teachings.

Claims 7-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of disorders of learning and memory, does not reasonably provide enablement for a method of treatment and/or prophylaxis of central nervous system diseases; a method of treatment and/or prophylaxis of disorders of perception, concentration; a method of prophylaxis of disorders of learning and memory. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The scope of the claims is not adequately enabled solely based on the activity related to cGMP activity provided in the specification. First, the instant claims cover disorders that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test procedures and assays are provided in the specification in pages 18-22 and *in vitro* concentration data for some of the exemplified compounds is provided in Table 1, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. The disorders encompassed by the instant claims include e.g., central nervous system diseases, disorders of perception, concentration, etc., some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Regarding cGMP mediated smooth muscle relaxation, a state of the art reference, Carvajal et al. (Journal of Cellular Physiology 2000) provides that “further investigation is necessary to elucidate the exact role of cGMP and PKG in the control of SM contractile activity in humans” (see page 417). Another reference, Yamashita et al. (Hypertension 2000) regarding cGMP-mediated vasorelaxation, indicates that “Although a large number of studies have tried to clarify the underlying mechanisms of nitrate tolerance, the precise mechanisms remain to be elucidated” (see page 100).

Claim 7 recites “treatment and/or prophylaxis of central nervous system diseases” which includes, Alzheimer's disease, dementia, hereditary cerebellar ataxias, paraplegias,

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syringomyelia, phakomatoses, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that “some degenerative diseases are difficult to classify because they involve multiple anatomic locations” (see page 2050). For example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that “[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease” (pg. 1994). Regarding the role of cGMP and NO in the central nervous system, Fisker et al. (PubMed Abstract enclosed) expressed that “The role of this pathway in the neuroregulation of growth hormone (GH) secretion has not yet been investigated”, thus showing the uncertainty in the field of interest of instant application.

The scope of the method claims is not adequately enabled solely based on the activity related to cGMP provided in the specification. The claim language includes diseases that are known and those that are yet to be discovered, for which there is no enablement. The instant claims are drawn to ‘A method of treatment and/or **prophylaxis** of....’ several diseases, and therefore, the instant claim language embraces disorders not only for the treatment, but also for “prevention” which is not remotely enabled. Based on the activity of the compounds to increase the cGMP levels in neurons (see specification pages 18-22), the instant compounds are disclosed to be useful, not only in treatment but also in “prevention” of central nervous system diseases, disorders of perception, concentration, learning and memory, for which applicants provide no competent evidence. “To prevent” actually means *to anticipate or counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant

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compounds can be administered in order to have the “prevention” effect. It is inconceivable based on the *in vitro* data related to cGMP activity, as to how the claimed compounds can, not only treat but also “prevent” the diseases of the instant claims. Further, there is no evidence on record which demonstrates that the *in-vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of ‘prevention’. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as “showing” such utility, and not “warranting further study”). Furthermore, there is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders encompassed by the instant claims.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 6-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. In the claims, it is recited that “A compound.... **and** the salts, solvates, **and/or** solvates of the salts thereof”, which is unclear because it is not clear if ‘a compound or a salt thereof is claimed **or** ‘a **mixture** of a compound and the salt’ is claimed. Replacing with -- A compound..... ~~and the~~ or a salts salt thereof – (throughout the claims) would overcome the rejection.
2. Claim 12 recites “A method claim 4 ...” and claim 4 is drawn to “A process ...”.

Consistent claim terminology is required throughout the claims.

Receipt is acknowledged of the Information Disclosure Statement filed on January 14, 2005 and a copy is enclosed herewith.

Conclusion


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Deepak Rao
Primary Examiner
Art Unit 1624

November 14, 2005